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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,661	GODDARD ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon, Ph.D	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *4-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/20/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. The Amendment and Declarations under 37 CFR § 1.132, both submitted 20 April 2005, have been entered. Claims 1-3 and 9-10 have been cancelled. Claims 4-8 and 12-13 are amended. Claims 14-17 are newly added. Therefore, claims 4-8 and 11-17 are under examination in the instant application.

2. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

3. The Office acknowledges the change in title.

4. The Applicants have provided a copy of the sequence listing in response to the "Notice to Comply".

5. Applicants request for correction of inventorship under 37 CFR 1.48(b) is acknowledged.

6. The Office acknowledges the submission of IDS dated 4/20/2005 and the additional information on BLAST searches.

Priority

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119. Applicants have argued that they are entitled to the benefit of the filing date of August 24, 2000 based on the disclosure in the PCT Application PCT/US00/23328 filed 8/24/2000 of the differential tissue expression distribution in tumor versus normal tissue (example 18). Although, the previous patent application(s) discloses the same polypeptide (SEQ ID NO: 136) and the nucleotides (SEQ ID NO: 135) encoding the polypeptide as the instant specification, the disclosure

is not enabling and because the disclosed function does not impart utility to the instant invention for the reasons set forth below and the previous Office Action dated 11 January 2005. Therefore, the filing date of 7 May 2002 is maintained as the priority date.

35 USC § 112, second paragraph, withdrawn

8. The rejection of Claims 1-13 under 35 U.S.C. 112, second paragraph, for being indefinite is withdrawn. Applicants' amendments to the current claims and remarks to clarify "extracellular domain" and "signal peptide" have necessitated the withdrawal (20 April 2005).

35 U.S.C. § 112, first paragraph, Written Description withdrawn

9. The rejection of claims 1-6 and 8-10 under 35 U.S.C. § 112, first paragraph, Written Description, is *withdrawn*. Applicants' amendments to the current claims and remarks to clarify "extracellular domain" have necessitated the withdrawal (20 April 2005).

35 U.S.C. § 112, first paragraph, Enablement withdrawn

10. The rejection of claim 6 under 35 U.S.C. § 112, first paragraph, scope of enablement, is *withdrawn*. Applicants' amendments to the current claims and remarks to clarify "extracellular domain" and have necessitated the withdrawal (20 April 2005).

35 U.S.C. § 101/112, first paragraph,

Lack of Utility, Enablement, maintained

11. The rejection of claims 4-8 and 11-17 under 35 U.S.C. 101, as lacking utility is maintained. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 4-9 of the previous Office Action (11 January 2005). The rejection of claims 4-8 and 11-17

under 35 U.S.C. 112, first paragraph is also maintained. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (11 January 2005), one skilled in the art clearly would not know how to use the claimed invention.

The Office acknowledges that the microarray experiments disclosed in the specification (example 18) does measure the level of mRNA expressed in tumor and normal controls. Thus, the Office will not respond to Applicants arguments with respect to both Pennica et al. and Sen et al. references. Applicants argue (20 April 2005, page 10) that the results presented in the instant specification are enabling for the polypeptide of SEQ ID NO: 136 (PRO1926). They argue that the utilities of PRO1926 polypeptide include the use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1926 cDNA is more highly expressed in normal esophagus tissue compared to esophageal tumor tissues counterparts. Applicant's arguments filed (20 April 2005) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing that polynucleotide is more highly expressed in normal esophagus tissue compared to esophageal tumor tissues counterparts. In addition, blast search provided asserts that PRO1926 is a secreted transmembrane polypeptide. There is no further supporting evidence to indicate that the polypeptide encoded by the polynucleotide of the instant invention is also differentially expressed in the normal tissue compared to the tumor tissue and as such one of skill in the art would conclude that it is not supported by a substantial

asserted utility or a well-established utility. Contrary to Applicants assertion that PRO1926 polypeptide is more highly expressed (20 April 2005, pages 14 and 15), Applicants only demonstrate more highly expressed cDNA for PRO1926 in normal esophagus tissue compared to esophageal tumor tissues counterparts. The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. There is no description in the specification to that would indicate a correlation with higher expression levels of the message to the PRO1926 polypeptide. It remains that, there is no information on the record as to whether the claimed protein is expressed at all in the skin tissue, cancerous or otherwise.

Given the increase in message (cDNA) for PRO1926 in the normal esophagus tissue compared to esophageal tumor tissues, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a more highly expressed mRNA would directly correlate with increased polypeptide levels. Further research needs to be done to determine whether the increase of PRO1926 cDNA in normal esophagus tissue compared to esophageal tumor tissues supports a role for the polypeptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the

> public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
>
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1926 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to their results, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that twenty-eight of the 165 protein spots (17%) or 21 of 98 genes (21.4%) had a statistically significant correlation

between protein and mRNA expression (abstract). In addition, it is stated that no significant correlation between mRNA and protein expression was found (r=-0.025) if the average levels of mRNA or protein among all samples were applied across the 165 protein spots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient also varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a subset of the proteins exhibited a significant correlation with mRNA abundance. Gygi et al. (1999, PTO1449 of 4/20/05) determined the correlation between mRNA and protein expression levels for selected genes expressed in yeast. It was found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data.

The declarations of Mr. Grimaldi, filed under 37 CFR 1.132 (20 April 2005), is insufficient to overcome the rejection of claims 4-8 and 11-17, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action. Similarly, the declaration of Dr. Polakis, filed under 37 CFR 1.132 (20 April 2005), is insufficient to overcome the rejection of claims 4-8 and 11-17, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action. Likewise, the declaration of Dr. Ashkenazi, filed under 37 CFR 1.132 (20 April 2005), is insufficient to overcome the rejection of claims 4-8 and 11-17, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

In the declaration filed under37 CFR 1.132 (20 April 2005, originally filed in application serial number 10/063,557), senior research associate Mr. Grimaldi has asserted that, if a difference in mRNA is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor tissues. It is further stated that additional studies can then be conducted if further information is desired. In paragraph 7, declarant indicates that the difference in the expression is expected to be reflected in the difference in the corresponding protein. However, there is no description in the specification to that would indicate a correlation with higher or lower expression levels of the message to the PRO1926 polypeptide.

Applicants further citing the second Grimaldi declaration (exhibit 2) filed under 37 CFR § 1.132 argues that, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed..... this same principal applies to gene under-expression." Citing paragraph 5, Applicants contend that "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for the diagnosis and treatment."

At paragraph 4 of the second Grimaldi declaration (Exhibit 2), the declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide)

as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1926 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO1926 gene is known to occur. All that the specification demonstrates is that the PRO1926 nucleic acid (mRNA) was more highly expressed in normal esophagus tissue compared to esophageal tumor tissues counterparts. No mutation or translocation of PRO1926 gene has been associated with for example, skin tumor. Therefore, in the absence of any of the above information, all that the specification does is present evidence that the mRNA encoding PRO1926 is more highly expressed in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the claimed polypeptides.

The Polakis declaration states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr Polakis characterizes the instances where such a correlation does not exist as exceptions to the rule.

The specification describes only mRNA expression data. The argument presented evinces that instant specification provides a mere invitation to experiment, and not readily available utility. Furthermore, as indicated above the literature cautions

researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (see Hu et al discussions above). It is also not known whether PRO1926 polypeptide is expressed in normal skin tissue. There is no nexus between the mRNA expression and PRO1926 polypeptide. In the absence of any of the above information, all that the specification does is present evidence that the mRNA encoding PRO1926 is present at higher levels in normal esophagus tissue compared to esophageal tumor tissues counterparts, and invite the artisan to determine the rest of the story. This is further borne out by Grimaldi assertion that "additional studies can then be conducted if further information is desired" (Appendix A, paragraph 7). Such is insufficient to meet the requirements of 35 U.S.C. § 101 utility for the claimed protein.

Although, Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide, it is important to note that the instant specification provides no information regarding protein levels. Only mRNA expression data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 4-8 and 11-17 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declarations do not provide data such that the examiner can independently draw conclusions. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, as discussed above in Hu et al. In

addition, as discussed above Haynes et al., Chen et al. and Gygi et al. disclose that the correlation between mRNA expression and protein expression is poor at best.

Applicants also contend that the claimed polypeptide would have diagnostic utility even if there is no positive correlation between gene expression and expression of the encoded polypeptide. Applicants assert that this position is supported by the declaration filed under 37 CFR 1.132 (20 April 2005) by staff scientist Ashkenazi. It claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (pages 1-2, Declaration, 20 April 2005) and to identify cancers for which there was an absence of gene product over-expression (page 2).

The declaration of Ashkenazi appears to argue that even if there was no correlation between gene expression and increased or decreased protein expression for PRO1926, the polypeptide encoded by a gene that is over-expressed or under expression in cancer would still have credible, specific and substantial utility. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not in the instant invention. Further research is required to determine such. Thus, the asserted utility is not substantial.

Applicants along with Mr. Grimaldi, Dr. Polakis and Ashkenazi declarations, Applicants also provide teachings from Molecular Biology of the Cell by Bruce Alberts and Genes VI (1997) by Ben Lewin, to support their assertion that there is a correlation between increased gene expression and increased protein expression (page: 19 and

20). Applicants also refer to additional articles by Zigang et al., and Meric et al. as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Zigang et al. describe a specific example of the expression of prostrate stem cell antigen (PSCA) protein and mRNA to validate it as potential molecular target for diagnosis and treatment of human prostrate cancer. It is asserted that the data shows " a high degree of correlation between PSCA protein and mRNA expression". Further Meric et al. states that "the fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. Meric et al also teaches that most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. It further states that gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability. Further reading of Meric et al. casts doubts on Applicants claim that there is a direct correlation between increased mRNA levels and the level of expression of the encoded protein. For example, the reference discusses that variations in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974). In addition, advances in technology allowing comparisons of message and protein using proteomics show a lack of correlation as evidenced by Haynes et al., Chen et al., and Gygi et al.

Applicants argue (Response, 20 April 2005, page 17) that even if a prima facie case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicants provide evidence in the form of a publication by

Hanna et al. (attached to the Response of 20 April 2005). Applicants contend that the publication teaches that the HER-2/neu (c-erbB2) gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicants argue that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically.

Applicants claim regardless of the cause of the differential expression, the fact that there is a higher level or lower level of expression PRO1926 gene in normal esophagus tissue compared to esophageal tumor tissues counterparts allows this mRNA expression to be used as a diagnostic tool. These arguments have been fully considered but are found to be partially persuasive because the Office accepts that aneuploidy has no relevance to the differential expression of the mRNA of the instant invention. However, the lack of information on the record whether the claimed protein (PRO1926) is expressed at all in normal skin tissues, cancerous or otherwise would make significant further research a necessity.

At page 14, Applicants assert that they have established that the accepted understanding in the art is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. Haynes et al. and Chen et al. teachings listed above and discussed contradict Applicants assertion that there exists a direct

correlation between mRNA levels and the level of expression of the encoded protein. In fact, the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues. Therefore, there is no evidence to support Applicants' assertion that there is working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels. The declarations and cited references do not establish a substantial utility for the claimed PRO1926 polypeptide molecules. As stated above, the specification does not provide sufficient guidance to the skilled artisan to diagnose or treat any disease.

A utility such as cancer research would in fact be specific to the polypeptide. However, further research is required to ascertain whether the protein levels of PRO1926 are altered and thus provide a substantial, that is, real-world and reasonable confirmed, utility. Therefore, all of these reasons, the rejection of claims 4-8 and 11-17 based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office Action is maintained.

35 USC § 112, first paragraph – Enablement, maintained

12. The rejection of claims 4-8 and 12-17 under 35 U.S.C. 112, first paragraph, because the specification does not enable one of skilled in the art to which it pertains, or with which it is most closely connected, to make and/or use the invention commensurate in scope with these claims. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 9-11 of the previous Office Action (11 January 2005). Even if the specification taught how to use the PRO1926 polypeptide (SEQ ID NO:

136), enablement would not be commensurate in scope with claims 4-6, and 12-17, which encompass % variants of SEQ ID NO: 136 (claims 4-5, for example), and various fragments of SEQ ID NO: 136 (claims 4-6, 14 and 15 for example).

Applicants are not enabled for polypeptides that have at least 95-99% identity to SEQ ID NO: 136 or the various fragments of SEQ ID NO: 136 because there is no structural or functional information provided in the specification. In addition, the lack of direction/guidance presented in the specification regarding which variants of polypeptides of SEQ ID NO: 136 would retain the desired activity, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the absence of working examples directed to variants and the breath of claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Although, Applicants have amended the claims to assert that the said polypeptide is highly expressed in normal esophagus tissue compared to esophageal tumor tissues counterparts or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophagus tissue compared to esophageal tumor tissues counterparts, there is no way of knowing which, if any variants would have the same property of higher expression in the specific tissue. There is no nexus between the degree of homology and regulation of gene expression. Until one identifies a particular variant that demonstrates a higher expression or not, one of skilled in the art would not know the expression profile of the variant. Modifications to the protein, e.g., by substitutions or deletions, would often result in deleterious effects to

overall activity and effectiveness of the protein. Similarly, there is no nexus between the degree of homology and the ability of the antibody (generated to polypeptide or fragments) to specifically detect the polypeptide of SEQ ID NO: 136 in skin tissue samples.

Accordingly, the disclosure fails to enable such a myriad of the claimed polypeptide molecules that not only vary substantially in length but also in polypeptide composition and to provide any guidance to one skilled in the art on how to make and use the claimed genus of polypeptide molecules. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed genus of the molecules embraced by the instant claims. Therefore, the rejection of record is maintained.

35 USC § 112, first paragraph – Written Description, maintained.

13. Claims 4-6, and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 11-13 of the previous Office Action (11 January 2005). Briefly, the Applicants were not in possession of all or a significant number of polypeptides that have 95-99% homology to SEQ ID NO: 136 and still retain the function of SEQ ID NO: 136.

Applicants discuss the legal standards applied when evaluating Written Description, including the requirement that written description depends on the nature of

the invention and the amount of knowledge imparted to those skilled in the art by the disclosure (page 21, 20 April 2005). The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case. However, Applicants have not described or shown possession of all polypeptides 95-99% homologous to SEQ ID NO: 136, that still retain the function of SEQ ID NO: 136. Nor have Applicants described a representative number of species that have 95-99% homology to SEQ ID NO: 136, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 136.

As discussed in the previous Office Action (11 January 2005) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1926 polypeptides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. Recitation of the phrase "wherein the polypeptide is more highly expressed in normal esophagus tissue compared to esophageal tumor tissues counterparts respectively, or wherein the said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal esophagus tissue compared to esophageal tumor tissues counterparts or antibody (generated to polypeptide or fragments) to specifically detect the polypeptide of SEQ ID NO: 136 in skin tissue samples," (amended claims, 20 April 2005), is not adequate to describe polynucleotides encoding the PRO1926 polypeptides that have 95-99% homology to the PRO1926 polypeptide, since there was no reduction to practice to support the amended claims.

Specifically, there is no way of knowing which, if any variants would have the same property of over-expression in the specific tissues. There is no nexus between the degree of homology and regulation of gene expression. Until one identifies a particular variant that is over-expressed or not, one of skilled in the art would not know the expression profile of the variant. The mere sequence alone will not allow one of skilled in the art to predict expression. Applicants made no variant polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

Claim Rejections - 35 USC § 102, maintained

14. Claims 4-8 and 11-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenzuela et al. (WO 00/55375, Pub. Date 09/00) is maintained. Applicants' arguments with respect to obtaining an earlier priority are not persuasive for reasons indicated above in paragraphs 7 and 11 because the disclosed function does not impart utility to the instant invention for the reasons set forth above and the previous Office Action. Thus, the filing date of 7 May 2002 is considered as the priority date. Therefore, the rejection of record is maintained.

16. No Claims are allowed.

17. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JANET ANDRES
PRIMARY EXAMINER

JS 06/05